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权利要求书1页 说明书6页 附图页数0页

[54]发明名称 [(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法

[57]摘要

本发明涉及的是可作为质子泵抑制剂药物的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法。将[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物溶解于碱性水溶液中,并使溶液为pH9-13,然后向该水溶液中滴加计算量的水溶性镁盐溶液,使沉淀充分并收集沉淀物。本发明方法克服和避免了须在有机相中合成的传统方法所带来的各种不利因素,简化了方法并大幅度降低了成本,尤其是大大有利于对环境和操作人员健康的保护。

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权 利 要 求 书

1. [(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于将[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物溶解于碱性水溶液中，并使溶液为 pH9-13，然后向该水溶液中滴加计算量的水溶性镁盐溶液，使沉淀充分并收集沉淀物。

2. 如权利要求 1 所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于所说的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物的碱性水溶液为 pH9-10。

3. 如权利要求 1 所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于所说的溶解[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物的碱性水溶液为碱金属氢氧化物的水溶液。

4. 如权利要求 1 所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于所说的水溶性镁盐为氯化镁或硝酸镁。

5. 如权利要求 1 至 4 之一所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于所说的水溶性镁盐的滴加量为[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物与镁离子的摩尔比为 1：0.45-0.55。

6. 如权利要求 1 至 4 之一所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于使所说的水溶性镁盐滴加完毕后的溶液 pH 为 7.5-8.5。

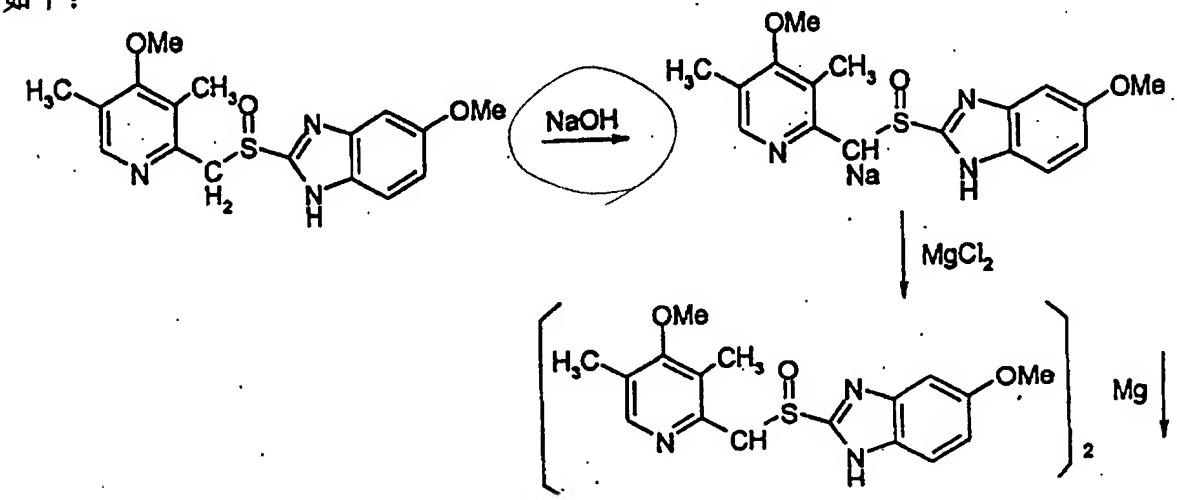
7. 如权利要求 1 至 4 之一所述的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法，其特征在于所说的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物为包括 R-和/或 S-奥美拉唑在内的奥美拉唑、兰索拉唑、泮托拉唑中的任何一种。

机溶剂为反应介质，特别有醇与钾、钠、镁等所成的有机金属化合物参与的反应，除反应的条件要求高，操作方法或工艺过程复杂，因而显著增加了在规模化生产上的难度外，有机溶媒的使用不仅将大大提高成本，并且会显著增大对周围环境及操作人员健康的损害和影响。此外，试验结果还显示，对从有机溶媒中制得的镁盐产物再用水处理而得到其相应水合产物的这一过程的控制也存在有一定的难度。因此，在能基本保持同等结果的情况下，一般均愿意采用并努力寻找以最常用的水为溶剂和/或尽可能温和条件的的制备方法，以尽量接近和符合“绿色”化学的发展要求。

发明内容

针对上述情况，本发明将提供一种以水为反应介质，在简单、方便和温和的反应条件下制备可以作为药用的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的方法。具体讲，是以水为反应介质一步即可得到同样的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐产品。这些化合物至少可以涉及目前已有报导可作为质子泵抑制剂类药物中的例如包括 R-和/或 S-奥美拉唑在内的奥美拉唑镁盐，以及兰索拉唑镁盐和泮托拉唑镁盐等化合物中的任何一种。

本发明所说的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的制备方法是，将[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物溶解于碱性水溶液中，并使溶液为 pH9-13，且最佳为 pH9-10，然后向该水溶液中滴加计算量的可溶性镁盐溶液使沉淀充分并收集沉淀物，即可得到相应的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐。以奥美拉唑镁盐为例的反应过程如下：



在上述方法中，所说用于溶解[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物的碱性水溶液，一般情况下建议采用碱金属氢氧化物的水溶液，如氢氧化钠、氢氧化钾等常用的碱金属氢氧化物，不仅方便易得外，而且可以尽量减少其它的杂质性离子或物质的引入，有利于后处理操作和提高产物的收率与纯度。

上述方法中所说的水溶性镁盐，作为实施例，例如可以使用氯化镁或硝酸镁等易得常用的镁盐水溶液。

由于在上述所说的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑化合物镁盐中，[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑化合物与镁离子成盐反应的理论计算量摩尔比为 1：0.5。因此，在碱性水溶液中所说的该[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑化合物与镁盐的成盐过程中，镁的加入量少于计算量必然导致成盐反应的不完全；而镁量加入过多，会有过多的氢氧化镁生成，也将明显增加后处理操作的复杂和困难，并影响所需产物的收率和纯度。试验结果显示，在兼顾这两方面的情况下，上述所滴加水溶性镁盐的计算量，一般采用使[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物与镁离子的摩尔比为 1：0.45～0.55 时，即可取得令人满意的结果。

如上所述，氯化镁等水溶性镁盐的加入量以及反应介质的碱性环境对成盐反应的结果都会产生影响。实验结果还显示，在上述的制备方法中，如能进一步使所说的水溶性镁盐滴加完毕后的反应溶液 pH 控制为 7.5-8.5，对反应产物的后处理以及产物的收率和纯度一般都能有满意的结果。

经反复实验显示，采用本发明上述制备方法所得到所说的[(取代的吡啶基)甲基]亚磺酰基-1H-苯并咪唑类化合物镁盐的收率及其纯度都是理想的，不会低于目前所用的有机溶媒法制备的结果，但由于采用的是最常用且不会带来任何污染影响的水为反应介质溶剂，反应条件温和，操作也十分简单，而且只经一步反应操作即同时完成成盐和相应的水合化反应，杂质成分的引入及副反应产物均大为减少，后处理操作也相应大为简化。这些显著的优越性除有利于反应本身及向工业化规模扩大生产外，对于保护环境以及保护操作人员身体健康，使化学工业和生产更加符合“绿色”化要求方面也具有极大的意义和价值。

以下再通过实施例形式的具体实施方式对本发明的上述内容作进一步的详细说明。但不应将此理解为本发明上述主题的范围仅限于以下的实施例，凡基于本

发明上述内容所实现的技术均属于本发明的范围。

具体实施方式

实施例 1

将 S-奥美拉唑 5 克（14.5 毫摩尔）加入 20 毫升水中，加入 10%氢氧化钠水溶液 6.7 毫升，搅拌使完全溶解后，溶液为 pH13，滴加氯化镁六水合物 1.47 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH8.1。析出的白色固定产物沉淀完全后，常规过滤，水洗涤沉淀后干燥，得 S-奥美拉唑镁盐产物，S-奥美拉唑的含量为 98.2%。

分析检测结果：

FT-IR(KBr)cm^{-1}：2997.7(Ar)，2949.6，2835.2(-CH_3,-CH_2-)，1616.2，1570.0，1271.2，1155.2，1077.6，839.0；

^{1}H-NMR(400MHz，DMSO) δ：2.16(s，3H)，2.22(s，3H)，3.68(s，3H)，4.24-4.28 (d，1H)，4.82-4.85(d，1H)，6.45-6.49(dd，1H)，7.03-7.07(d，1H)，7.31-7.33(d，1H)，8.27(s，1H)：；

XRD(2θ)°：5.70(15.49)，6.45(13.69)，7.43(11.90)，12.69(6.99)，16.62(5.33)。

实施例 2

将 S-奥美拉唑 5 克（14.5 毫摩尔）加入 20 毫升水中，加入 10%氢氧化钠水溶液 10 毫升，搅拌使其完全溶解后，溶液为 pH13，滴加氯化镁六水合物 1.47 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH8.4。析出的白色固定产物沉淀完全后，过滤，常规方式用水洗涤沉淀后干燥，得 S-奥美拉唑镁盐产物，S-奥美拉唑的含量为 85%。

实施例 3

将 S-奥美拉唑 5 克（14.5 毫摩尔）加入 20 毫升水中，加入 10%氢氧化钠水溶液 6.5 毫升，搅拌使完全溶解后，溶液 pH13，滴加氯化镁六水合物 1.47 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH8.0。析出的白色固定产物沉淀完全后，常规过滤，水洗涤沉淀后干燥，得 S-奥美拉唑镁盐产物，S-奥美拉唑的含量为 99.1%。

实施例 4

将 S-奥美拉唑 5 克（14.5 毫摩尔）加入 20 毫升水中，加入 10%氢氧化钠水溶液，搅拌使完全溶解后，溶液 pH13，滴加氯化镁六水合物 1.47 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH8.2。析出的白色固定产物沉淀完全后，常规方式过滤，水洗涤沉淀后干燥，得 S-奥美拉唑镁盐产物，S-奥美拉唑的含量为 98.7%。

实施例 5

将奥美拉唑混旋体 5 克（14.5 毫摩尔）加入 20 毫升水中，搅拌下滴加 10%氢氧化钠水溶液至全部溶解后，滴加硝酸镁六水合物 1.86 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH7.8。析出的白色固定产物沉淀完全后，常规方式过滤，水洗涤沉淀后干燥，得混旋的奥美拉唑镁盐产物。

实施例 6

将泮托拉唑 5 克（14.2 毫摩尔）加入 20 毫升水中，搅拌下滴加 10%氢氧化钠水溶液至全部溶解后，溶液为 pH9.4，滴加氯化镁六水合物 1.44 克（7.08 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH7.8。析出的白色固定产物沉淀完全后，常规方式过滤，水洗涤沉淀后干燥，得泮托拉唑镁盐产物。

实施例 7

将 S-奥美拉唑 30 克（86.8 毫摩尔）加入 120 毫升水中，搅拌下滴加 10%氢氧化钠水溶液至 pH12 使全部溶解后，滴加氯化镁六水合物 8.82 克（43.4 毫摩尔）的水溶液 50 毫升并充分搅拌约 30 分钟，pH8.0。析出的白色固定产物沉淀完全后，常规方式过滤，水洗涤沉淀后干燥，得 S-奥美拉唑镁盐产物，含量 99.1%。

实施例 8

将兰索拉唑 5 克（13.5 毫摩尔）加入 20 毫升水中，搅拌下滴加 20%氢氧化钠水溶液至全部溶解后，溶液为 pH10，滴加氯化镁六水合物 1.38 克（6.79 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH7.9。析出的白色固定产物沉淀

完全后，常规方式过滤，水洗涤沉淀后干燥，得兰索拉唑镁盐产物。

实施例 9

将 R-奥美拉唑 5 克（14.5 毫摩尔）加入 20 毫升水中，加入 10%氢氧化钠水溶液，搅拌使完全溶解后，溶液为 pH13，滴加氯化镁六水合物 1.47 克（7.23 毫摩尔）的水溶液 10 毫升并充分搅拌约 30 分钟，pH8.3。析出的白色固定产物沉淀完全后，常规方式过滤，水洗涤沉淀后干燥，得 R-奥美拉唑镁盐产物，含量为 98.1%。

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Patent Agent: Pu Jia-wei

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Drawings: 0 page

[54] **Title of Invention**:

Process for Preparing Magnesium Salt of [(Substituted pyridyl)methyl]sulfinyl-1H-benzimidazole Type Compound

[57] **Abstract**:

The present invention relates to a process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol, which can be used as a medicine of a proton pump inhibitor. The compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol was dissolved in an alkaline aqueous solution, and the pH value of the solution was made to 9-13, then it was added into the aqueous solution by dripping a calculated amount of a water-soluble magnesium salt solution, it was thoroughly precipitated and the precipitate was collected. The process of the present invention overcomes and avoids various disadvantages coming with the traditional processes of synthesizing in organic phases, and the process is simplified and the costs were reduced significantly, and it is especially advantageous in protecting the environment and the health of the operators.

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Claims

1. A process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol, characterized by adding the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound into an alkaline aqueous solution and making the solution be pH9 to pH13, then adding a calculated amount of a water-soluble magnesium salt solution by dripping into the aqueous solution, precipitating the same thoroughly and collecting the precipitate.

2. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in claim 1, characterized in that said alkaline aqueous solution of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound is pH9 to pH10.

3. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in claim 1, characterized in that said alkaline aqueous solution which dissolves the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound is an aqueous solution of alkali metal hydroxide.

4. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in claim 1, characterized in that said water-soluble magnesium salt is magnesium chloride or magnesium nitrate.

5. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in one of claim 1 to 4, characterized in that the added amount by dripping of said

water-soluble magnesium salt is that a molar ratio of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound to magnesium ions is 1:0.45 to 0.55.

6. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in one of claim 1 to 4, characterized in that the solution's pH is 7.5 to 8.5 after the adding of said water-soluble magnesium salt by dripping has been completed.

7. The process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol as claimed in one of claim 1 to 4, characterized in that said [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound comprises any one of omeprazole, including R- and /or S- omeprazole, lansoprazole and pantoprazole.

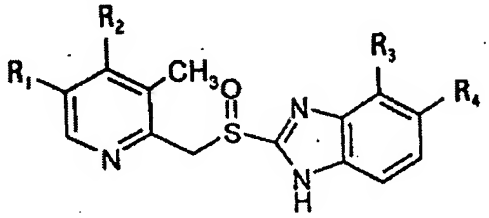
Process for preparing Magnesium Salt of [(Substituted pyridyl)methyl] sulfinyl-1H-benzimidazole Type Compound

Technical Field

The present invention relates to a process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol, which can be used as a medicine of a proton pump inhibitor.

Background art

It has now been found that compounds of the type of [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol of a structure formula (I), such as omeprazoles (II), particularly S-omeprazole in them, as well as lansoprazole (III) and pantoprazole (IV), etc., and the magnesium salts of these compounds, are a type of medicine which can be used as a proton pump inhibitor, which can inhibit gastric acid secretion efficiently, and can be used as an anti-ulcer agent for preventing and treating diseases that relate to gastric acid in mammals, particularly in human.



(I)

wherein, (S-, R-, and an enantiomer mixture) omeprazole (II):

R_1=CH_3, R_2=OCH_3, R_3=H, R_4=OCH_3,

lansoprazole (III): R_1= H, R_2=OCH_2CF_3, R_3=R_4=H,

pantoprazole (IV): R_1= H, R_2=OCH_3, R_3= $OCHCF_2$, R_4=H.

Taking magnesium salt of omeprazole as an example, there have been relevant reports regarding the preparation processes of the magnesium salts of these

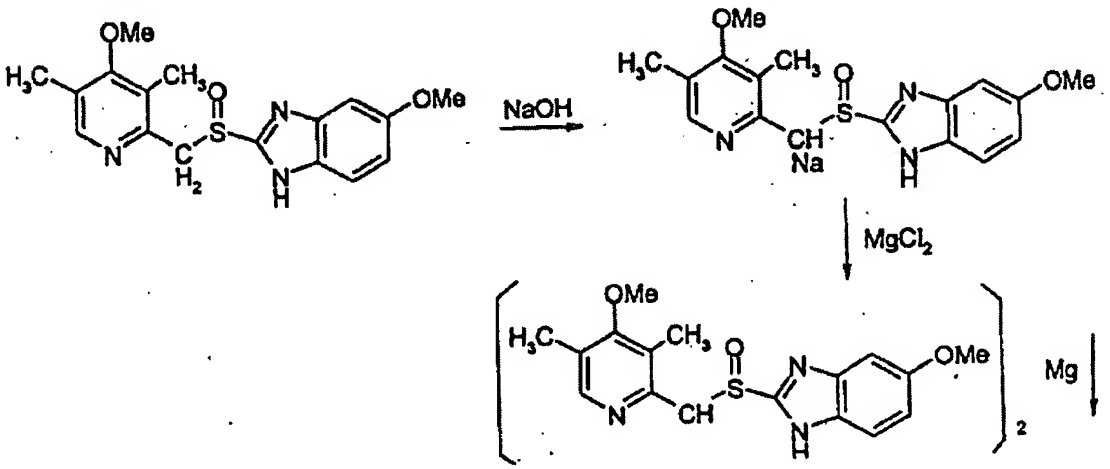
compounds, and what is common in them is that all of them need to have their basic reaction processes carried out and completed in an organic solvent, and then treated in an aqueous solution. For example, it is described in the patent literatures such as publication number CN 1126993A and CN 1258295A and some relevant patent literatures that, after the potassium or sodium salt of omeprazole in an organic solvent has been transformed into a corresponding magnesium salt by using a magnesium source, such as magnesium alkoxide, etc., it is separated from the organic solvent and then relevant aftertreatments are carried out in an aqueous solution. It is well known that, in reactions using an organic solvent as the reaction medium, particularly when participated by organic metal compounds formed by alcohol and potassium, sodium, magnesium and the like, besides the facts that the requirements to reaction conditions are high, the operating process or the technical process are complicated, therefore the difficulties in scaling up the production are significantly increased, the use of the organic solvent not only significantly increases the costs, but also significantly increases damages and effects to the environment and the health of operators. Furthermore, the test results have also shown that, there are also difficulties presented in the control of the process, in which the magnesium salt product obtained from the organic solvent is treated with water to obtain its corresponding hydrated product. Therefore, provided it can achieve basically the same results, it would be generally desirable to use and make efforts to find a preparation process using the most commonly used water as a solvent and/or in the conditions as mild as possible, so as to approach and meet the developing requirement of "green" chemistry as far as possible.

Contents of the invention

Aiming at the above-mentioned situation, the present invention is to provide a process for preparing a medicinal magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol by using water as a reaction medium under simple, convenient and mild reaction conditions. More

specifically, the same product of magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol can be obtained with one step by using water as the reaction medium. These compounds can at least relate to any of the currently reported compounds that can be used as a proton pump inhibitor, for example, they can be any one of the magnesium salts of omeprazoles including R- and/or S-omeprazole, magnesium salt of lansoprazole and magnesium salt of pantoprazole, etc.

Said process for preparing a magnesium salt of a compound of the type of [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol of the present invention is as follows, dissolving the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound into an alkaline aqueous solution, making the pH value of the solution to 9-13, preferably be pH9-10, then adding into the aqueous solution by dripping a calculated amount of a water-soluble magnesium salt solution, having it thoroughly precipitated and collecting the precipitate so as to obtain the corresponding magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound. By taking the omeprazole magnesium salt as an example its reaction process is as follows:



In the above-mentioned process, said alkaline aqueous solution used for dissolving the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound is generally

advised to use an aqueous solution of alkali metal hydroxide, such as the commonly used alkali metal hydroxide like sodium hydroxide, potassium hydroxide and the like, which are not only easily available, but also can reduce the introduction of other impurities of ions and substances, which is advantageous to the operate of aftertreatments and to increase yield and purity of the product.

Said water-soluble magnesium salt in the above-mentioned process, as an embodiment, for example can use an aqueous solution of magnesium salt that is easily available and commonly used, such as magnesium chloride or magnesium nitrate.

Since in the above-mentioned magnesium salt of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound, the theoretically calculated value of molar ratio of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound to magnesium ions in the salification is 1:0.5. Therefore, during said salification of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound and magnesium salt in the alkali aqueous solution, if the added amount of magnesium is less than the calculated amount, it will certainly lead to the incomplete salification; while an excess addition of magnesium will lead to excess production of magnesium hydroxide, which also increases the complication and difficulties of the aftertreatment operation and influences the yield and purity of the required product. The experimental results have shown that, by giving considerations to the two cases, a molar ratio of 1:0.45 to 0.55 of the [(substituted pyridyl)methyl] sulfinyl-1H-benzimidazol compound to the magnesium ions is generally used as the calculated amount of the dripping aqueous solution mentioned above, which has achieved a satisfactory result.

As mentioned above, both the added amount of the water-soluble magnesium salt such as magnesium chloride and the like, and the alkaline environment in the reaction medium will have effects on the result of the salification. The

experimental results have also shown that, in the above-mentioned preparation process if the pH value of the reaction solution can be further controlled within 7.5 to 8.5 by the completion of adding said water-soluble magnesium salt by dripping, the aftertreatments of the reaction product and the yield and purity of the product can generally achieve satisfactory results.

Repeated experiments have shown that both the yield and purity of said magnesium salt of the [(substituted pyridyl)methyl]sulfinyl-1H-benzimidazol compound produced by using the above-mentioned preparation process according to the present invention are ideal, and are not lower than the results by the currently used organic solvent process, however, due to the use of water as the reaction medium solvent, which is most commonly used and does not introduce any contaminant, the reaction conditions are mild and the operation is also quite simple, furthermore, the salification and the corresponding hydration can be completed at the same time with a one-step reaction, both the introduction of impurities and the side reaction products are reduced significantly, and the aftertreatment operation is also significantly simplified. These significant advantages are not only beneficial to the reaction itself and to the scaling-up of the production to an industrial scale, but also have great importance and value in protecting the environment and the health of the operators, and in making the chemical industry and production better meet the "green" requirements.

Hereinbelow, the above-mentioned contents of the present invention will be further described in details by the following embodiments in the form of embodying examples. But it should not be understood as that the subject matter of the present invention mentioned above is limited to the following embodiments, any technique realized on the basis of the above-mentioned contents of the present invention is within the scope of the present invention.

Embodiments

Embodiment 1

5g (14.5 mmol) of S-omeprazole was added into 20 ml of water, then 6.7 ml of 10% of sodium hydroxide aqueous solution was added therein under stirring to dissolve completely, the solution was at pH13, and then 10 ml of aqueous solution of 1.47 g (7.23 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 8.1. After the separated white solid product precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of S-omeprazole, with a content of S-omeprazole at 98.2%.

The results of the analysis measurement are as follows:

FT-IR(KBr)cm^{-1}: 2997.7(Ar), 2949.6, 2835.2(-CH_3, -CH_2-), 1616.2, 1570.0, 1271.2, 1155.2, 1077.6, 839.0;

^{1}H-NMR(400MHz, DMSO)δ: 2.16(s, 3H), 2.22(s, 3H), 3.68(s, 3H), 4.24-4.28(d, 1H), 4.82-4.85(d, 1H), 6.45-6.49(dd, 1H), 7.03-7.07(d, 1H), 7.31-7.33(d, 1H), 8.27(s, 1H):;

XRD(2θ)° : 5.70(15.49), 6.45(13.69), 7.43(11.90), 12.69(6.99), 16.62(5.33).

Embodiment 2

5g (14.5 mmol) of S-omeprazole was added into 20 ml of water, then 10 ml of 10% of sodium hydroxide aqueous solution was added therein under stirring to dissolve completely, the solution was at pH13, and then 10 ml of aqueous solution of 1.47 g (7.23 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 8.4. After the separated white solid precipitated completely, it was filtered, then the precipitate was washed with water and dried in a conventional way, to obtain a product of magnesium salt of S-omeprazole, with a content of S-omeprazole at 85%.

Embodiment 3

5g (14.5 mmol) of S-omeprazole was added into 20 ml of water, then 6.5 ml of 10% of sodium hydroxide aqueous solution was added therein under stirring to dissolve completely, the solution was at pH13, and then 10 ml of aqueous solution of 1.47 g (7.23 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 8.0. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of S-omeprazole, with a content of S-omeprazole at 99.1%.

Embodiment 4

5g (14.5 mmol) of S-omeprazole was added into 20 ml of water, and then an aqueous solution of 10% sodium hydroxide was added therein, stirred to dissolve completely, the solution was at pH13, then 10 ml of aqueous solution of 1.47 g (7.23 mmol) of magnesium chloride hexahydrate was drop-added and stirred sufficiently for about 30 minutes, the pH was 8.2. After the separated white solid precipitated completely, it was filtered commonly, then washed the precipitate with water and dried, to obtain a product of S-omeprazole magnesium salt, with a content of S-omeprazole of 98.7%.

Embodiment 5

5g (14.5 mmol) of an omeprazole enantiomer mixture was added into 20 ml of water, and then an aqueous solution of 10% sodium hydroxide was added by dripping under stirring until dissolved completely, then 10 ml of an aqueous solution of 1.86 g (7.23 mmol) of magnesium nitrate hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 7.8. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of an omeprazole enantiomer mixture.

Embodiment 6

5g (14.2 mmol) of pantoprazole was added into 20 ml of water, then an aqueous solution of 10% sodium hydroxide was added by dripping under stirring until dissolved completely, the solution was at pH9.4, then 10 ml of an aqueous solution of 1.44 g (7.08 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 7.8. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of pantoprazole.

Embodiment 7

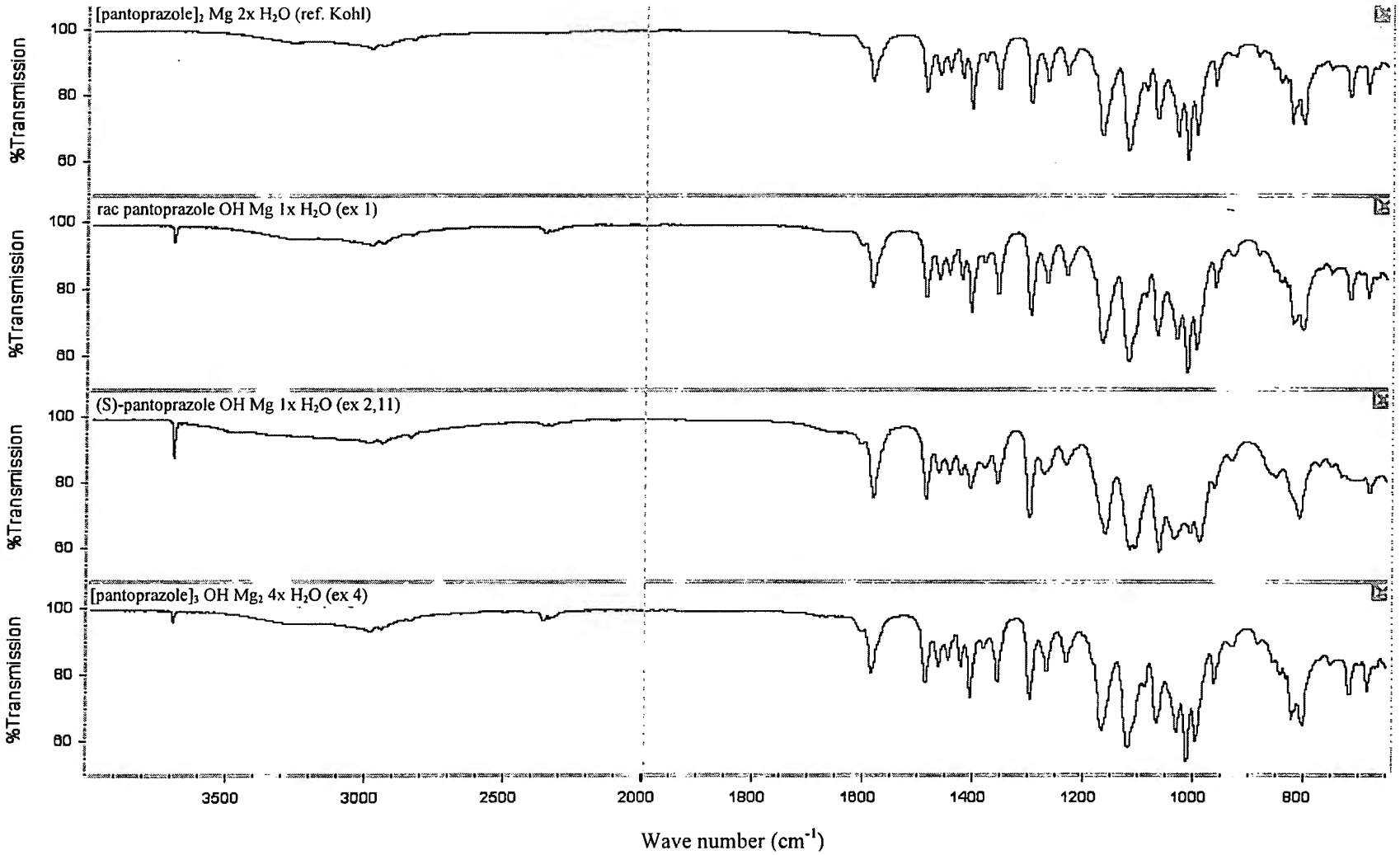
30g (86.8 mmol) of S-omeprazole was added into 120 ml of water, then an aqueous solution of 10% sodium hydroxide was added by dripping under stirring until pH12 to dissolve completely, then 50 ml of an aqueous solution of 8.82 g (43.4 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, the pH was 8.0. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of S-omeprazole, with a content of 99.1%.

Embodiment 8

5g (13.5 mmol) of lansoprazole was added into 20 ml of water, then an aqueous solution of 20% sodium hydroxide was added by dripping under stirring until dissolved completely, the solution was at pH10, then 10 ml of an aqueous solution of 1.38 g (6.79 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, the pH was 7.9. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of lansoprazole.

Embodiment 9

5g (14.5 mmol) of R-omeprazole was added into 20 ml of water, and then an aqueous solution of 10% sodium hydroxide was added by dripping under stirring until dissolved completely, the solution was at pH13, then 10 ml of an aqueous solution of 1.47 g (7.23 mmol) of magnesium chloride hexahydrate was added by dripping and thoroughly stirred for about 30 minutes, and the pH was 8.3. After the separated white solid precipitated completely, it was filtered in a conventional way, then the precipitate was washed with water and dried, to obtain a product of magnesium salt of R-omeprazole, with a content of 98.1%.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rac pantoprazole OH Mg 1x H2O (ex 1)
(S)-pantoprazole OH Mg 1x H2O (ex 2,11)
[pantoprazole]3 OH Mg2 4x H2O (ex 4)
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60
3500
3000
2500
2000
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1600
1400
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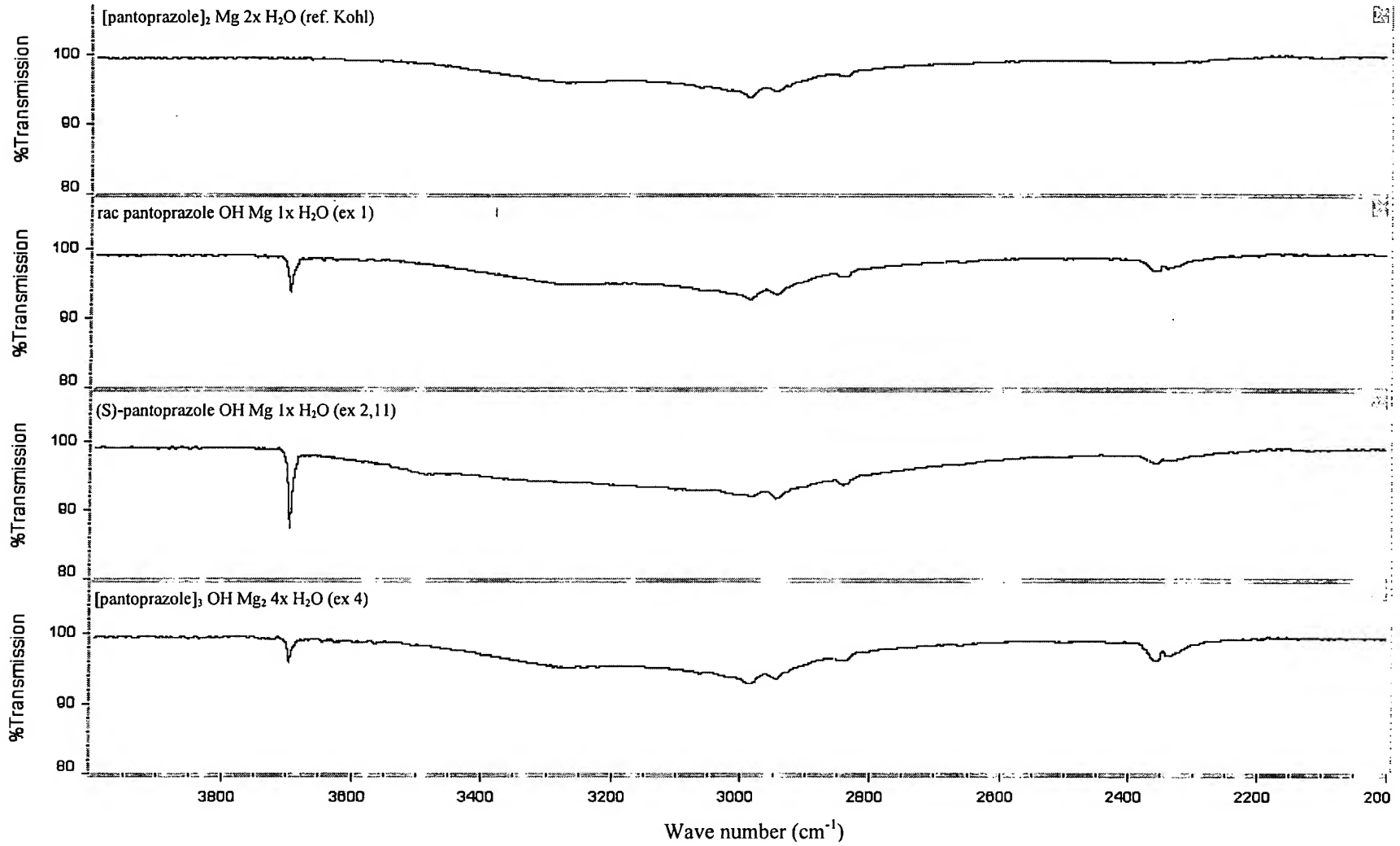
[pantoprazole]2 Mg 2x H2O (ref. Kohl)
rac pantoprazole OH Mg 1x H2O (ex 1)
(S)-pantoprazole OH Mg 1x H2O (ex 2,11)
[pantoprazole]3 OH Mg2 4x H2O (ex 4)
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80
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3600
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2400
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